**Considerations in the Integration of Study Results for the Assessment of Concern for Human Reproductive and Developmental Toxicities**

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## 1. Overall Decision Tree Process

This document proposes an approach to aid in the integration of clinical and non-clinical information (i.e., reproductive and general toxicology, pharmacokinetic and ADME (absorption, distribution, metabolism and elimination) findings for therapeutic agents in the assessment of human development and reproductive risks. This document is being issued for discussion purposes only. After discussion of the proposal, it will be developed into a guidance document in accordance with FDA's Good Guidance Practices, 62 FR 8961 (February 27, 1997).

The proposed integration process attempts to assess the "probability" or "likelihood" of an adverse reproductive outcome in humans based on data drawn from multiple species. Perceived concern for human reproductive risks is independent of the nature of the response or the reversibility or repairability of the response. The nature of the reproductive risk, along with the severity and reversibility of the response is considered in the "clinical management" of therapeutic use in the context of reproduction.

Prior to the use of this approach, the studies carried out to assess the safety of the therapeutic agent[1] should have been thoroughly evaluated. The ability of the therapeutic to exhibit positive signals of toxicity in the completed studies should have been determined and the strength of any positive signal should have been evaluated. In addition, an evaluation of pharmacodynamic effects, a comparison of animal and human metabolic and disposition data, a comparison of animal and human toxicologic effects, and a comparison of exposures in non-clinical studies relative to the highest proposed clinical exposure of the therapeutic should all have been completed. For some therapeutics (e.g., vaccines and cytotoxic agents) there may be exceptions to the type(s) and extent of the toxicologic data generated, based on the biologic actions and test systems available for studying these compounds.

Positive signals may be broadly categorized as **reproductive** or **developmental** toxicities. For the purpose of this document, the category of **reproductive toxicity** is subdivided into three subclasses, *fertility and fecundity*, *parturition*, and *lactation*. The four subclasses of **developmental toxicity** are, *developmental mortality*, *dysmorphogenesis*, *alterations to growth*, and *functional toxicities*. Each of these endpoints will be discussed under sections, 1.1 and 1.2 which follow. Whenever a signal is identified for any subclass of reproductive effect (whether in valid reproductive or general toxicology studies, or from human use studies), it should be independently evaluated to estimate the concern for human reproductive and/or developmental risks. Flowcharts, which present schematic representations of the integration process for reproductive and developmental toxicities are presented and discussed in sections 2-4, which follow.

**1.1) Reproductive Toxicities** encompass structural and functional alterations that may affect reproductive competence in the $F_0$ generation. These are subdivided into three

1 For the purpose of this document, a 'therapeutic agent' may be either a 'drug' or 'biologic'.

subclasses: *fertility and fecundity*, *parturition*, and *lactation*.

**1.1.1) Fertility and Fecundity*:*** Therapeutics administered to animals may alter reproductive competence. Evidence of toxicity to male reproductive competence may be seen as degeneration and/or necrosis of the reproductive organs, reduction in fertility and sperm count, alterations to sperm motility and/or morphology, aberrant mating behavior or altered ability to mate, alterations to endocrine function, etc. Similarly, toxicity to female reproductive competence may involve the reproductive organs, alterations to endocrine regulation of gamete maturation and release, effects on mating behavior and/or ability to mate. Diminished fertility in females is typically detected by reductions in the fertility index, the number of implantation sites, time to mating, and fecundity.

**1.1.2) Parturition:** Reproductive toxicities affecting labor and delivery in animals may be manifested as changes in the onset or duration of parturition. Changes to the duration of parturition are frequently reported as mean time elapsed per pup, or total duration of parturition.

**1.1.3) Lactation*:*** Therapeutics administered to lactating animals may be a source of unwanted "therapy" to the developing organism. Additionally, therapeutics may alter the process of lactation (e.g., the quality and/or quantity of milk) or the maternal behavior towards the nursing offspring.

**1.2) Developmental Toxicities** are generally those that affect the $F_1$ generation. These are divided into four subclasses: *developmental mortality*, *dysmorphogenesis*, *alterations to growth*, and *functional toxicities*.

**1.2.1) Developmental Mortality:** Toxicities causing mortality to the developing conceptus may be evident at any time from early conception to weaning. Thus, a positive signal may appear as pre- or peri-implantation loss, early or late resorption, abortion, stillbirth or neonatal death.

**1.2.2) Dysmorphogenesis:** These effects are generally manifested as malformations and/or structural alterations to the skeleton or soft tissues of the offspring.

**1.2.3) Alterations to Growth:** These effects are generally defined by growth retardation, although excessive growth or early maturation may also be considered an alteration to growth. The most common metric for growth is body weight. Additionally, crown-rump length, ano-genital distance, and age of belano-preputial separation or vaginal patency may be measured.

**1.2.4) Functional Toxicities*:*** Although these toxicities include any persistent

alteration of normal physiologic or biochemical function, usually only developmental neurobehavioral endpoints are measured, such as: learning, memory and the development of reflexes (e.g., time to navigate mazes, times to conditioned avoidance learning, development of the righting response, acoustic startle response, etc.).

## 2. Initiation of the Integration Process (Flowchart A)

For any therapeutic, studies may have been conducted to evaluate the potential for none, some, or all of the above mentioned toxicities. When studies have been conducted, the outcome may be a positive signal or no signal for any of the reproductive or developmental toxicities. Flowchart A depicts the sequential decisions to be made in evaluating the various scenarios that may be encountered. Within this flowchart are 3 questions or decisions which need to be addressed: a) were animal or human reproductive toxicity studies conducted with the therapeutic and are they available for comprehensive evaluation, b) were the test systems used to evaluate the reproductive potential of the therapeutic appropriate, and c) were positive effects or no signals detected in the test species? Each of these questions and possible outcomes are presented in sections 2.1-2.3 which follow.

### 2.1) Availability of Studies

In Flowchart A, the first question to be asked is "were studies carried out to assess individual reproductive or developmental toxicities and are the detailed study results available for comprehensive evaluation?"

In the event that no studies were conducted with the therapeutic, or the detailed study results are not available for comprehensive evaluation, then it should be explained that studies were not done, or were otherwise unavailable, to adequately assess risk to human reproduction. However, if reproductive toxicity studies were conducted and are available for comprehensive evaluation, then the assessment process continues in Section 2.2.

### 2.2) Relevance of Test System or Route of Administration

In this section, the question to be asked is "were relevant studies carried out to assess the reproductive or developmental toxicities of the therapeutic?"

If the test system was not relevant to the assessment of the risk for therapeutic induced reproductive effects in humans, it is recommended that an explanation as to why the studies were not relevant or were otherwise inappropriate be provided (i.e., due to improper test species, non-relevant route of drug administration, etc.). All supporting information pertaining to study relevance should be discussed. Flowcharts B and C should not be used to evaluate endpoints derived from “non-relevant” or otherwise

"inappropriate" reproductive toxicity studies, regardless of whether the studies demonstrated positive or no signals.

If the reproductive toxicity studies conducted with the therapeutic are relevant to the human condition and the proposed therapeutic use, then the decision process should continue in section 2.3.

**2.3) Relevant Test System with Positive or No Signal**

If no signals were seen for an endpoint in a test system considered relevant and appropriate to humans, then the evaluation process should continue in Section 3 (Flowchart B) for study evaluation.

In the event that a positive signal was seen for an endpoint in a test system considered relevant and appropriate to assess the reproductive risk to humans, then the evaluation process should continue in Section 4 (Flowchart C) for data integration and risk evaluation.

## 3. Reproductive or Developmental Endpoints with No Signal (Flowchart B)

The evaluation of reproductive and/or developmental endpoints for which no adverse effects have been observed is a "step-wise" or "hierarchical" process of decision-making leading to a recommendation regarding the certainty with which no adverse reproductive effects in humans would be expected. A graphic representation of the decision tree process for reproductive endpoints, which show No Signal, is presented in Flowchart B.

In many instances only a single non-clinical study will be available for the evaluation of reproductive endpoints (i.e., ICH endpoints A-B and D-F). However, multiple studies may be available for any reproductive endpoint, and would be expected for the evaluation of the dysmorphogenic potential of the therapeutic. The availability of multiple studies for any reproductive toxicity endpoint then raises the issue of inter-study "concordance" or "non-concordance" of results, which will be discussed in Section 4 of this document (pertaining to the evaluation of reproductive endpoints with a Positive Signal). Flowchart B should be used only if the results of all studies addressing a particular reproductive or developmental endpoint are negative. If an endpoint was positive in any general or reproductive toxicology study, then Flowchart C (Section 4) should be used for the assessment of the level of concern for human reproductive risk.

The following questions should be addressed in the evaluation of therapeutics demonstrating no adverse effects on a subclass of Reproductive or Developmental Toxicities.

### 3.1) Model System Predictive Adequacy

Is the model test system likely to be predictive of the human condition? This question may be further characterized by the following points:

a) Do the test species (or test systems) demonstrate or have the capability of demonstrating the pharmacologic effect(s) of the therapeutic?
b) Do the test species (systems) demonstrate an overall toxicity profile, which has been generally predictive of the human toxicity profile induced by the therapeutic?
c) Do the test species (systems) demonstrate pharmacokinetic and ADME profiles for the therapeutic which are relatively similar to those demonstrated in humans?

If the answer to any of these questions is “no,” then the product assessment should include a statement that the animal study(ies) conducted with the therapeutic may not be adequate to evaluate the risk for adverse human reproductive effects. A description of the inadequacies of the test system should also be provided. If however, the overall answer to this series of questions is "yes," then the risk integration process should continue with questions regarding the adequacy of study conduct (Section 3.2).

### 3.2) Study Conduct Adequacy

Were the studies adequately conducted to assess the endpoint? This question may be further characterized by the following points:

a) Were adequate doses (concentrations) of the therapeutic compound administered to the test species/system (e.g., MTD, MFD, etc.)?
b) Were the exposures (based on AUC, $C_{max}$, or other appropriate systemic exposure metric) achieved in the test species (or test systems) significantly greater than those demonstrated in humans at the maximum recommended human dose?

If the answer to either or both of these questions is “no,” then the risk evaluation for the therapeutic should contain a statement that the animal studies conducted were potentially inadequate to fully evaluate the risk for adverse human reproductive effects, along with a description of the situation. If however, the overall answer to this series of questions is “yes,” then the evaluation process should continue with Section 3.3.

### 3.3) Class Alert

If there is a Class Alert for the compound (based on a related chemical structure, reactive metabolic intermediate or pharmacologic effect), then the appropriate class specific information should be included in the risk evaluation and discussion of the therapeutic. Class alerts should be based on adverse reproductive effects previously demonstrated in humans by closely related chemical entities or compounds with similar pharmacodynamic effects.

If there are no Class specific concerns related to the therapeutic, then the evaluation process should continue in Section 3.4.

### 3.4) Signals in Related Reproductive and Developmental Subclasses

Was a positive signal of toxicity detected for any other endpoint within the same category of reproductive or developmental toxicities? The lack of an observed effect for any individual reproductive or developmental endpoint may not necessarily imply that there is no risk for adverse human effects for that (or a related) endpoint. A signal for any other endpoint within the same broad category of reproductive or developmental toxicity may suggest some human risk for other endpoints within the category, for which no signals were seen in the animal studies. For example, if a therapeutic caused alterations to growth or dysmorphogenesis in one (or more) animal species, then it may be inappropriate to conclude that no risk of fetal mortality exists for humans exposed to the therapeutic. Likewise, a therapeutic that disrupted the hormonal regulation of fertility or parturition in animals might cause an effect on lactation in humans (even if no effects were observed on lactation in animals). In both cases, it may be inappropriate to conclude that the underlying mechanisms of toxicity may not be demonstrated as a categorically related toxicity in humans (even though effects on these specific endpoints were not observed in the animal studies).

If the answer to this question is "no" (effects on other endpoints within the category were not seen), then the evaluation should state that there is no predicted risk for adverse human effects regarding this category of endpoints (i.e., if no form of developmental toxicity was demonstrated in the animal studies, then the evaluation should state that there is no predicted risk of developmental mortality, dysmorphogenesis, alterations to growth, or functional toxicities in humans exposed to the therapeutic, based on the results of animal studies). However, if adverse effects on other endpoints within the category were observed in the animal studies, then the evaluation should state that there was no observed effect on the incidence of the specified endpoint in studies conducted in animals. For the positive reproductive and developmental endpoints detected in the animal toxicology studies, the risk evaluation process for the therapeutic should proceed in Section 4 of this document (Flowchart C).

The following scenarios and potential actions are possible outcomes of the evaluation:

a) The animal model and dose selections were considered appropriate, there is no class specific alert for the therapeutic or a related compound, and no adverse effects on categorically related endpoints were observed.

Based on the animal studies, it appears reasonable to conclude that there is no predicted risk for adverse reproductive effect (for the category) in humans.

b) Other therapeutics in the same pharmacologic class have demonstrated adverse reproductive effects in humans.

While the results of adequately conducted developmental and reproductive toxicity studies in animals were negative, some concern remains for adverse reproductive effects in humans exposed to the therapeutic. Any discussion of the therapeutic should present the reprotoxicity study results for the compound, along with a discussion of the class relevant effects of similar therapeutics.

c) Exposure to the therapeutic in the animal reproduction studies was not significantly greater than the maximal recommended human exposure.

Although the results of developmental and reproductive toxicity studies in animals were negative, some concern remains for adverse reproductive effects in humans exposed to the test compound. Presentation of the reproductive toxicity findings as negative in animals should include a discussion of the relative interspecies therapeutic exposure levels and the impact this may have on the ability to detect signals relevant to humans.

d) The animal models were not considered appropriate for testing of the therapeutic (e.g., the test species lacked the cellular receptors responsible for the pharmacologic activity of the therapeutic, or did not demonstrate a toxicity or metabolite profile similar to the human).

Some concern remains for potential adverse reproductive effects in humans exposed to the therapeutic. Any discussion of the therapeutic should present the reproductive toxicity study results along with a discussion of their possible inaccurate identification of potential hazard to humans.

e) No adverse effects were seen for multiple reproductive endpoints, at exposure levels significantly greater than expected in humans, and when tested in animal models considered appropriate for predicting the human response. However, adverse effects were seen in animals on one or more categorically related reproductive endpoints.

Some concern remains for adverse reproductive effects in humans exposed to the therapeutic. The risk evaluation for the product should state only that no adverse effects on the specified endpoints were observed in studies conducted in animals, and should continue with the risk assessment for the positive endpoint (Section 4; Flowchart C).

**4. Reproductive or Developmental Endpoints with a Positive Signal (Flowchart C)**

Six factors may affect the level of concern with which a positive signal is perceived. Each of the factors is in turn made up of one or more contributory elements, which contribute to the overall evaluation and conclusion regarding the factor. The first factor, Signal Strength is composed of six contributory elements. To ensure that each contributory element is given due consideration, integration across the Signal Strength factor should be subdivided into Signal Strength, Part A and Signal Strength, Part B, each of which is comprised of 3 contributory elements. Thus, within the integration tool (Flowchart C), the six columns represent the six integration factors. These six factors are: 1) Signal Strength, Part A; 2) Signal Strength, Part B; 3) Pharmacodynamics; 4) Metabolic/Toxicologic Concordance; 5) Relative Exposure; and 6) Class Alerts.

It is important to note that adequate human pregnancy outcome data are considered separately from the non-clinical findings and may dramatically influence the overall assessment of human risk of reproductive toxicity.

Each factor and its respective contributory elements should be evaluated independently and integrated into the overall risk evaluation. The implicit assumption of this integrated analysis is that the process begins with a positive signal that is evident in one or more of the examined species (either in a reproductive toxicology study or an effect on a reproductive tissue/system/behavior in a general toxicology study). Assessment within any one of the individual factors should not be an arithmetic summation of the contributory elements, but an integration made with regard for the quality and nature of the data under consideration. The overall assessments of risk for each of the six factors should be assigned unitary values of +1, -1 or 0, if the factor is perceived as increasing, decreasing or having no effect on the level of perceived risk for reproductive or developmental effects. Conclusions regarding the six factors should be summed to arrive at an overall level of concern for human reproductive risk

Intra- or inter-species concordance of adverse effects deserves some special consideration in this risk integration process. Not all species or individual animals within a species are equally sensitive to any given toxic insult. Therefore, intra-species concordance of effects may be demonstrated by the occurrence of related adverse effects across dose groups (i.e., a reduction in normal growth parameters at one dose may be related to an increased incidence of developmental mortality at a higher dose). Similarly, a spectrum of responses should be considered when evaluating the concordance/non-concordance of effects observed between different test species. In general, concordance of responses within or between species may be evaluated using the two broad categories of reproductive and developmental toxicity. A positive signal in one dose group or species potentially may be considered concordant with a related categorical effect in another dose group or species.

Intra- and inter-species concordance/non-concordance of observed effects should be considered in the estimation of human risk of adverse reproductive outcomes. If a specific type of reproductive or developmental toxicity (i.e., lactation effects or developmental delays) has been demonstrated in two or more animal species, it may logically be assumed that a similar effect represents the most likely adverse event to be seen in humans treated with the drug. In the event that dissimilar but related adverse effects within the two major categories of reproductive and developmental effects are

detected in multiple test species (i.e., alterations to growth in one species and developmental mortality in another, or parturition effects in one species with lactation effects in the second), it may be assumed that some level of risk of the related endpoints (toxicities) within the category may be demonstrated in human reproduction. (For the circumstance where a signal is seen for only one endpoint within a category, see section 3.4)

A detailed discussion of the proposed reproductive risk integration process, the individual factors, their contributory elements, and the assignment of the risk level is contained in the following paragraphs (Sections 4.1-4.6).

**4.1) Signal Strength, Part A**. A positive signal from individual or multiple species (e.g. *fertility and fecundity*, *dysmorphogenesis*, etc.) should be analyzed with respect to three contributory elements: 1) Cross-Species Concordance, 2) Multiplicity of Effects, and 3) Adverse Effects as a Function of Time.

**4.1.1) <u>Cross-Species Concordance</u>** - The observation of analogous hazards in more than one species (provided that the therapeutic was evaluated in multiple species) constitutes the defining characteristic of cross-species concordance. Cross-species concordance is most likely to be identified for dysmorphogenesis or developmental mortality, since these toxicities are frequently detected in the 'organogenesis' testing paradigm in which multiple species are typically evaluated. Additionally, sub-chronic and chronic toxicity studies in rodents and non-rodents may indirectly identify alterations to endocrine function or gonadal histopathology which predictably alter fertility. When cross-species concordance is observed, concern for this contributory element is enhanced. Concern is diminished when a signal is detected in only one species (with the proviso that the negative species is an appropriate animal model, and that studies were adequate in design, dosing, and implementation).

Conversely, peri- and postnatal studies are conventionally conducted only in a single species, and therefore, cross-species concordance for alterations to parturition or lactation may not be available. In such cases, the identification of a positive signal will have to be evaluated using the single species data, omitting questions specifically addressing multiple species concordance/non-concordance of effects.

**4.1.2) <u>Multiplicity of Effects</u>** – Multiplicity of effects is defined by the observation of two or more effects within any one of the seven reproductive or developmental endpoints (defined at the beginning of this document) for a single animal model/species. Examples of multiple targets manifested as two or more positive signals within a single category of toxicity include *dysmorphogenesis* involving tissues of multiple embryonic origins (e.g., defects affecting soft tissue, skeletal tissue, and/or neural tissue); and drug effects on both the onset, duration and/or outcome of *parturition*. When all species examined demonstrate multiplicity of effects, concern for adverse human reproductive outcomes is enhanced. When signals from two [or more] species

are present, but multiplicity of effects is observed only in one, concern is unchanged. Should neither species exhibit multiplicity of effects, then concern for adverse human reproductive effects is diminished for this contributory element.

**4.1.3) <u>Adverse Effects as a Function of Time</u>** - An adverse event may occur during one or more stages of reproductive competence or development. Concern for this contributory element is enhanced when the toxic effect is observed in more than one stage of reproduction/development. For example, developmental mortality may be reported as early or late resorptions, abortions, or stillbirths. Generally, concern for adverse reproductive effects in humans is enhanced when adverse effects in animals are seen in multiple stages of development, and are unchanged or diminished when adverse effects are observed only during a single and discreet interval. Moreover, it is important to define the timing of the period of susceptibility for the adverse event, if this is possible, based on the experimental results.

**4.2) Signal Strength, Part B.** As a second component in the assessment of signal strength, a positive signal should be analyzed with respect to the ensuing: 1) co-existence of maternal toxicity, 2) presence of a dose-response relationship, and 3) the observation of rare events.

**4.2.1) <u>Maternal Toxicity</u>** - When evaluated in a single test species, any effect occurring at doses which are not maternally toxic elicits enhanced concern. Conversely, concern will generally be diminished when the adverse effects are observed only in the presence of frank maternal toxicity, provided that the adverse reproductive effect may be reasonably attributed to the maternal toxicity.[2] This applies to all seven subclasses of reproductive and developmental toxicity.

When analyzing outcome from two or more species, which may be reasonably attributed to maternal toxicity, the overall assessment of concern should be based on a composite analysis of the data from all adequately studied species. For example, concordance between the species of adverse reproductive effects in the absence of maternal toxicity results in an enhanced level of concern, whereas interspecies concordance of effects seen only in the presence of clear maternal

[2] The attribution of the adverse fetal effect(s) to maternal toxicity will generally be assumed to be based on previously collected data delineating the relationship between the maternal and reproductive effects. However, the magnitude of the adverse effect demonstrated in the offspring versus the severity of the toxicity demonstrated in the dam, may be considered when drawing a conclusion as to the potential significance of the effect for humans.

toxicities results in a conclusion of diminished concern. Non-concordance between the test species as to the presence and relevance of maternal toxicities may result in no change in the overall level of concern for this contributory element.

In the event that one species is considered inappropriate to the analysis, then the evaluation should be performed as for a single species (as discussed in the preceding paragraph).

**4.2.2) Dose-Response Relationship** – The perception of concern is enhanced for compounds that evoke any of the following: a) an increase in the severity of effects with an increase in dose, b) an increase in the incidence of animals affected with an increase in dose, or c) a high incidence of effects across all dosed groups. Conversely, concern is diminished or unchanged when the observed effects do not fit within the classifications defined above.

When data are available for more than one species, only one of which demonstrates a dose-response relationship, concern will generally be unchanged. A clear dose related increment in fetal adverse effects in both species enhances the level of perceived concern, whereas the lack of any dose response effect in all species diminishes the level of concern for this contributory element.

**4.2.3) Rare Events** - Observations that are known to occur spontaneously with a low frequency in the test species are considered rare. It is recognized that developmental toxicity studies conventionally lack the statistical power to detect subtle increases in rare events. Thus, reports that rare events are observed with increased frequency among drug-exposed animals are cause for enhanced concern; however, the absence of rare events does not diminish concern. For example, concern is enhanced when rare events are detected in one or more species (even if another species fails to demonstrate an effect).

**4.3) Pharmacodynamics**. Subclasses of toxicity, for which positive signals were detected, should be analyzed with respect to two contributory elements: 1) the therapeutic index, and 2) the similarity between the pharmacologic and toxicologic Mechanisms.

**4.3.1) Therapeutic Index (TI)** - The purpose of the determination of the TI is to define the extent of the overlap of the dose response functions for toxicity and efficacy. Since it is rare that complete determinations of the dose- or concentration dependent toxicity and efficacy curves will be defined in a single species, the use of estimations or surrogate endpoints may be necessary in this evaluation. To reduce the impact of variation in the steepness of the dose-response curves on the process, estimation of the

TI should be based on comparison of the $TD_{10}$ and the $ED_{90}$ concentrations.[3]

When the $TI_{10/90}$ is < 5, the concern for human risk is enhanced. Conversely, when the $TI_{10/90}$ ratio is > 20, concern for adverse human reproductive effects is diminished. Concern for reproductive risks in humans is unchanged when the $TI_{10/90}$ ratio falls between 5 and 20.

In the event that data are available for the determination of the $TI_{10/90}$ ratios in multiple species, the assessment of risk for this contributory element should be based on an integrated analysis of data from all adequately studied species. Concordance between the species in the size of the $TI_{10/90}$ may result in enhancement, diminishment or no change in concern as defined for a single species. In the event of non-concordance of the TI ratios between multiple test species, the nature of the toxic endpoints observed and the relevance of the endpoint and test species to the human condition should be considered before making an assessment. In the event that one species is considered inappropriate to the analysis, then the evaluation should be performed as for a single species.

**4.3.2) <u>Similarity between Pharmacologic and Toxicologic Mechanisms.</u>** Concern is enhanced when the adverse effect represents an extension, progression or related response to the intended pharmacologic effect of the therapeutic. Examples would be the delay of parturition by drugs known to suppress uterine smooth muscle contractility, or an observation of hypotension in the offspring of dams treated during late gestation with a drug known to lower blood pressure.

**4.4) Concordance Between the Test Species and Humans.** Concordance between the test species should be analyzed with respect to the following: 1) the metabolic and drug disposition profiles, and 2) the general toxicity profiles of the test species and humans.

**4.4.1) <u>Metabolic and Drug Disposition Profiles</u>** - Drug disposition, elimination and bio-transformation (pathways and metabolites) in the test species and humans should be evaluated. Generally, reproductive toxicities

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[3] The $TD_{10}$ (toxic dose or concentration) should be defined by the $C_{max}$ (or other appropriate exposure metric) which produced the toxic reproductive response in 10% of a "responsive" or "sensitive" species, whereas the $ED_{90}$ (efficacious dose or concentration) should be defined by the $C_{max}$ (or other appropriate exposure metric) which produced the desired effect in 90% of the test species. Preferably, both the $TD_{10}$ and $ED_{90}$ should be defined in the same species. However, in some instances estimation of the $ED_{90}$ may be based on in vitro cell inhibition studies (frequently seen for antibiotics and antineoplastic agents), or efficacy data derived from another species (i.e., estimates of efficacious drug concentrations may only be available in humans). The same exposure metric should be used in the estimation of the $TD_{10}$ and $ED_{90}$ values. Scientific justification for the drug exposure metrics used for comparison should be provided.

induced by compounds with similar metabolic and distribution profiles in animals and humans are of greater concern. It is not necessary that the profiles be identical between the species, as qualitative similarities may be equally informative. Concern for compounds with highly dissimilar metabolic/distribution profiles in animals and man is unchanged or diminished (the latter occurs when the toxic effect seen in the test species may be attributed to the non-human metabolite). However, quantitative differences in metabolic profiles between the test species and humans should not be over interpreted, as this is a relatively common occurrence.

When there are significant differences in the drug distribution and metabolic profiles between several species, yet each species demonstrates a similar adverse reproductive or developmental toxic effect, then the toxic endpoint is likely attributable to the parent drug or a common bio-transformed product. In this case, where data to support the attribution of the toxic effect to a non-human drug metabolite is not available, then the assumption should be that the toxic effects observed in the animals are relevant to the human. Concern for adverse human reproductive effects would likely be enhanced in this circumstance.

**4.4.2) <u>General Toxicity Profiles</u>** - Concern for reproductive and developmental toxicities is enhanced when the overall toxicity profile of a therapeutic, as seen in one or more animal species, is similar to that in humans. In contrast, non-concordance between the animal and human findings in the general toxicology studies may lead to a conclusion of diminished concern. When general toxicology data are available for multiple species used for reproductive toxicity assessment, the determination of enhanced, diminished or no change in concern for human reproductive risk should be based on the integrated assessment of each test species ability to duplicate human adverse effects in response to the therapeutic.

**4.5) Relative Exposures.** Cross-species comparison of systemic drug exposure (at LOAEL and NOAEL) based on the relevant metric (e.g., AUC, $C_{max}$, $C_{min}$, BSA adjusted, or nominal dose) are critical determinations. In general, concern is increased for relative exposure ratios (animal:human) that are $\leq$10, and are decreased for exposure ratios $\geq$25. Ratios between 10-25 are not associated with any change in the perception of concern for this factor. When applicable, the sum of the parent compound and its metabolites should be considered in the assessment of relative exposures.

Similar to the previous discussions of interspecies concordance, available data for multiple test species should be considered in the overall assessment of concern for the human condition. Thus, if exposure is low ($\leq$10 fold) in multiple species, concern is increased, whereas if relative exposure is high ($\geq$25 fold) the level of concern is decreased. In the event a significant difference in relative exposures is observed between multiple test

species, the appropriateness of the metric (for example, AUC, Cmax) being used to define the inter-species exposure comparisons should be assessed. If the use of alternative metrics fails to reduce the disparity between species, then the assessment of risk should be based on the most sensitive species.

Relative interspecies exposure data may need to be evaluated in light of species-specific differences in protein binding, differences in receptor affinity and differences in free drug concentrations. In the absence of meaningful differences between the test species and humans in either protein binding or receptor affinity, relative exposure comparisons may be based on total drug concentration.

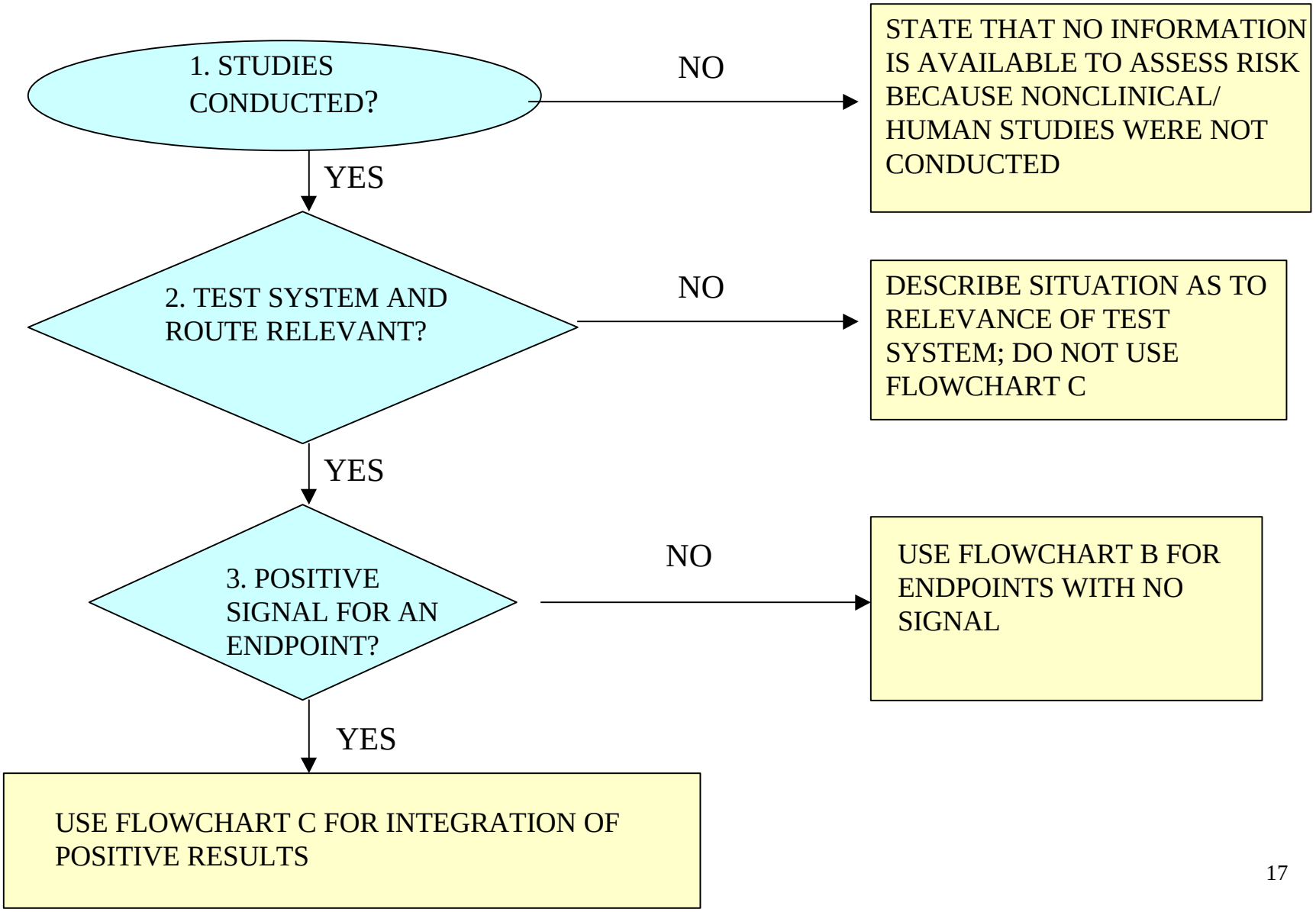
**4.6) Class Alerts.** The determination of a class alert, based on a related chemical structure, reactive metabolic intermediate or pharmacologic effect, should be determined based on data from prior human experience. In general, the perception of concern is increased when the reproductive toxicity seen in the animals is evoked by a drug from a class of compounds (structure or pharmacologic effect) known to produce adverse reproductive effects in humans. A decreased concern for human risk should occur only under those circumstances in which a class of compounds, although demonstrating adverse effects in animals, has been previously shown to have no adverse effects on human reproduction. In the absence of human reproduction data for the drug class or related agents, the assessed level of concern for human reproduction will be unchanged.

**4.7) Summary/Integration of Positive Findings.**
Technical notes on the use of the Integration Tool (Flowchart C)

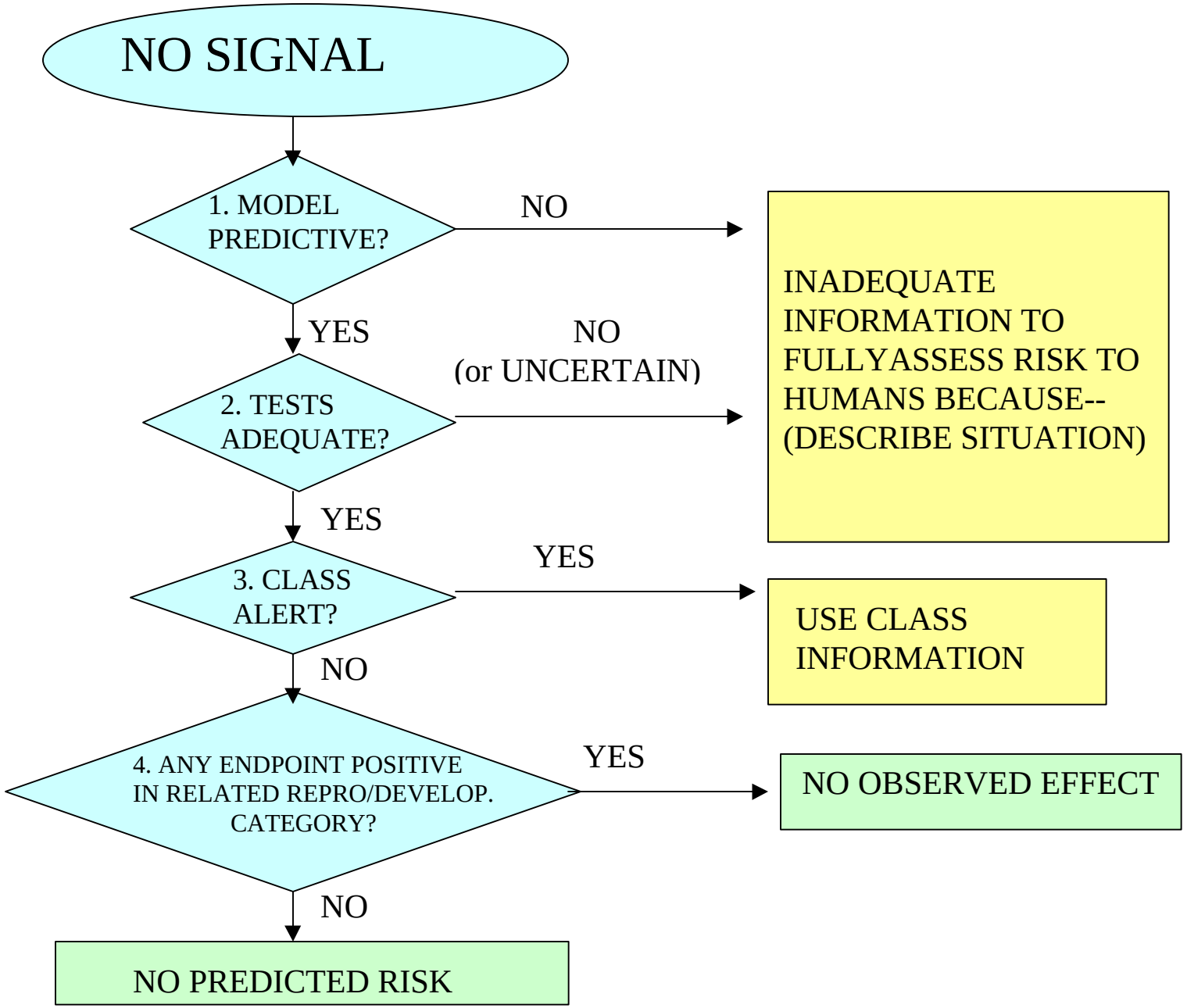
1) When a positive finding for developmental or reproductive toxicity is encountered in non-clinical reproductive or general toxicology studies, there is a perceived concern regarding the toxicity. In order to evaluate the appropriateness and level of such concern, positive findings from each of the seven subclasses of reproductive and developmental toxicity should be subjected to separate assessments of risk. All information regarding a particular subclass of reproductive endpoint, regardless of the species of origin, and which contributes to a specific positive finding, should be considered in the risk evaluation.

2) The assignment of concern for each of the six factors of the integration tool, reflects a weight of evidence assessment taking into account the quality and nature of the data under consideration for each of the contributory elements within the factor. The assignment of concern for any factor should not be determined by an arithmetic summation of its contributory elements. The result of the assessment for each factor should be an overall assignment of increased (+1), decreased (-1), or no change (0) in the level of concern for human reproductive risk. The values for the six factors should then be summed to arrive at an overall conclusion of "significant concern," "low concern," or "no known concern" for human reproductive risk for each of the seven developmental or reproductive endpoints. When sufficient information regarding the therapeutic is available to address each of the six factors within Flowchart C, a net value of > +3 should be suggestive of a significant degree of concern for human reproductive risk (for the endpoint under evaluation), whereas a value < -3 should be considered suggestive of no known concern for human reproductive risk.

# FLOWCHART A. OVERALL DECISION TREE FOR EVALUATION OF REPRO/DEVELOPMENTAL TOXICITY RISK



FLOWCHART B. DECISION TREE FOR ENDPOINTS WITH NO SIGNAL



*SIGNALS*

A. REPRODUCT. TOXICITY
1. Fertility & fecundity
2. Parturition
3. Lactation

B. DEVELOP. TOXICITY
1. Develop. mortality
2. Dysmorphogenesis
3. Alterations to growth
4. Functional toxicity

# FLOWCHART C. INTEGRATION OF POSITIVE REPRO/ ANCILLARY STUDY RESULTS